REMARKS

1. Amendments to the Claims

Claims 27-30 and 32-36 are pending. Claim 33 is amended to add a space. Claim 35 is herein amended to incorporate base claim 30 and to be independent. New claim 37 is added. Support for new claim 37 is found in the Specification at page 9, lines 11-14.
No new matter has been added.

2. Supplemental Interview Summary

Applicants again sincerely thank Examiners Niebauer and Gupta for granting Applicants' representatives the courtesy of an Interview on July 7, 2010. Applicants' representatives filed an Interview Summary on July 14, 2010, and the Examiner filed an Interview Summary on July 22, 2010.

With regard to the Examiner's Summary, Applicants respectfully suggest that they have already presented and have discussed evidence that shows that there was no reasonable expectation of success in substituting PlGF protein for the adenovirus expression vector taught by Hattori. This evidence has been presented with the Gianni Declaration. Applicants present further evidence as discussed below.

During the Interview, Applicants also reiterated that the claims recite "consisting of". Applicants also emphasized the arguments presented in the last response, *i.e.*, that the Examiner's reasoning is incomplete because one of skill in the art, based on the ineffectiveness of the administration of PlGF protein alone, shown by the experimental results in the Specification, would have no reason to combine PlGF with GCSF, and if they did would expect only the effect of GCSF alone.

Applicants again thank the Examiners for their time and consideration of the present application.

3. Rejections under 35 U.S.C. § 103, obviousness

The Examiner rejects claims 27-30, 32, and 34-36 as unpatentable over Robinson, Merck Manual, and Hattori. The Examiner also rejects claims 27-30, 32, and 34-36 as unpatentable over Robinson, the Merck Manual, and Hattori, and further in view of Anderlini and Carmeliet. Applicants respectfully traverse.

(a) The claims exclude the administration of Hattori.

As pointed out in the Interview, the claims recite "a pharmaceutical composition consisting of" GCSF and PlGF in combination with suitable excipients and/or adjuvants. (Claim 27) However, Hattori does not administer a pharmaceutical composition "consisting of" PlGF. Instead, the composition of Hattori is an adenovirus vector and not a protein at all.

Moreover, an adenovirus vector would materially affect the basic and novel characteristics of the claimed methods. Thus, the Hattori does not administer a composition "consisting essentially of" the protein PlGF, as required by claim 35. Moreover, the administration is not of the protein itself, but instead of the "machinery" to make the protein in situ.

Thus, a PlGF protein is not administered in Hattori. Accordingly the combined references do not disclose or suggest every element of the claimed invention, and so they fail to establish *prima facie* obviousness of the invention.

For at least these reasons Applicants request that the rejection be withdrawn.

(b) The Examiner's rationale is based on an incorrect assumption and an incorrect legal standard.

Applicants submit that the Examiner has applied an improper legal standard. The Examiner first uses the references to make a case for *prima facie* obviousness, *i.e.*, that the combined prior art references teach or make obvious, either explicitly or implicitly, every element of the claimed invention. Applicants can then provide evidence or arguments to rebut the case of *prima facie*

obviousness. If this includes evidence of unexpected results, the Examiner is supposed to weigh the evidence of unexpected results against the strength of the *prima facie* case. MPEP 716.01(d).

"The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker,* 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it. With regard to rejections under 35 U.S.C. 103, the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a prima facie case of obviousness) is more probable than not." MPEP § 2142.

While Applicants do not concede that the Examiner has established *prima facie* obviousness, Applicants submit that the Examiner has improperly analyzed the issues of obviousness in view of the Specification and the Gianni Declaration.

The Examiner asserted that the combination of Hattori and Robinson teach every element of the claimed invention. In response, Applicants provided the Gianni Declaration which affirmatively states that:

1) an administration of PlGF protein alone is ineffective,
2) one of skill in the art would recognize that administration of PlGF protein is different from administration of an Ad-PlGF vector which then expresses PlGF protein,
3) the administration of the combination of PlGF and GCSF leads to a synergistic effect, *i.e.*, one that is more than additive.

In the Response dated November 13, 2009, Applicants argued that point 1) rebuts the assertion that one of skill in the art would have expected that PlGF protein to be effective. Since this is the basis for the Examiner's conclusion that one of skill would have been motivated to combine

administration of PlGF protein with GCSF protein, the evidence also rebuts the presumption that one of skill in the art would have thought that the administration of GCSF and PlGF would be more effective than GCSF alone.

However, the Examiner did not weigh the evidence of unexpected results. Instead the Examiner asserts that since "predictability is determined at the time of the invention" one of skill would have expected PlGF protein to be effective and thus, would have also used it in a combination therapy with GCSF. (Office Action, page 10) The Examiner also states "[t]here is nothing of record to show that the data of the applicant is prior art." (Office Action, page 11) Applicants submit that the emphasis on the timing of the data is an improper inquiry.

Applicants' own data, either in the Specification or provided post-filing, is not prior art. The Specification is entitled to some level of deference as it evidences both the standard of the art at the time of filing, and the invention. In addition, the Declaration is entitled to deference as a sworn statement by a practitioner of skill in the art, who is not an Examiner and who is not an attorney. But the Examiner disregards these statements.

Furthermore, if administration of PlGF does not work now, there is no reason to believe that administration of PlGF would have worked in the past. Therefore, the Examiner's deliberate disregard of the data presented in the Specification and the Declaration amounts to an error of law.

(c) The sustained, localized, production of PlGF by cells transformed by the Ad-PlGF vector in Hattori provides significantly different results from the injection of a bolus of PlGF protein *per se*, as shown by the results in the Specification.

The Examiner states that whether one skilled in the art would recognize that administration of Ad-PlGF is different from administration of PlGF protein is essentially irrelevant because one of skill in the art would learn from Hattori that PlGF protein "augments the number of circulating

hematopoietic cells and that the mobilization of hematopoietic cells followed by the kinetics of placental growth factor plasma elevation." (Office Action, page 11)

But this assertion ignores the point made by Dr. Gianni, the data in the Specification, the teachings of Robinson, and the knowledge in the art as evidenced by the Rafii paper (attached).

Dr. Gianni explains that kinetics of a bolus injection of PlGF protein would not be the same as an Ad-PlGF system. (Declaration, page 2) Accordingly, one of skill in the art would have no idea of the particular kinetics of a bolus injection of PlGF protein, or the effectiveness of such.

The Specification teaches that administration of PlGF protein alone is ineffective. Thus, **if one of skill in the art were to have applied the logic of the Examiner, and tested the PlGF protein, he or she would have known that PlGF (administered as a protein) was ineffective.**

Robinson "recognize that rapid clearance is a disadvantage of recombinant molecules and that a goal is to achieve clinical efficacy with fewer injections. . . . Thus one would be motivated to look for alternate strategies and techniques to achieve such a goal." (Office Action, page 4) Applying the Examiner's statements to the art at issue, Applicants submit that one of skill would have looked for alternate strategies, such as administration of an adenovirus vector, rather than simply combining two proteins.

That the state of the art at the time of the invention was made would have led one of skill to choose an adenovirus vector administration, rather than administration of a protein, is supported by further writings of Hattori. The attached paper by Rafii, Heissig, and Hattori indicates that the total amount of a cytokine in the plasma is important, and the gradient of the cytokine is "most likely critical for the induction of chemokinesis and motility of stem cells" (Rafii et al., Gene Therapy (2002) 9, 631-641, at 635, left col. line 57-58, of which Hattori is an author). In addition the paper states that adenovirus vectors "can produce large titers of a chemokine . . . in extramedullary sites to promote mobilization of BM-derived stem cells," indicating that large

titers of chemokine in specific locations are required for stem cell mobilization (Rafii et al., page 635, left col., lines 60-62). However, Rafii et al. state that required locoregional delivery of membrane or matrix-bound stem cell-active cytokines "**is not possible by conventional injection of recombinant proteins**" (Rafii et al., page 635, right col., lines 3-6). Thus, it is clear that Hattori, as one skilled in the art, had come to the conclusion that the administration of a protein for the mobilization of stem cells would be ineffective.

Accordingly, Applicants reiterate that it is clear based on the prior art of record, contemporaneous scientific papers, statements from one of skill in the art, and the Specification that one of skill in the art would have understood that administration of PlGF protein would not be effective to increase the circulating colony forming blood cells, circulating long term colony initiating blood cells, or white blood cells. Thus, one of skill in the art would have no reasonable expectation that the combination of PlGF with GCSF would have more than merely additive results. As the results shown in the Specification are much better than additive, and are unexpected to one of ordinary skill in the art who reads Robinson, the Merck Manual and Hattori, the present invention should be found unobvious over these references. Applicants accordingly request that the rejection be withdrawn.

(d) The Examiner has failed to explain how "0 (the results obtained with PlGF protein injection) + 1 (the results of GCSF injection) = 4 (the result of injection of PlGF protein with GCSF)" is not an unexpected result sufficient to overcome any *prima facie* case of obviousness that is deemed established by the combination of the references cited.

Applicants submit that the Examiner has failed to explain why the results obtained with the combination of GCSF and PlGF are not unexpected. Applicants submit that GCSF and PlGF together elicit synergistic effects. However, the Examiner suggests that one of skill in the art would expect at least a 20-fold increase over a negative control (*i.e.*, no PlGF), based on Hattori. However, this conclusion is again predicated on the assumption that one of skill in the art would expect PlGF protein to be effective alone. As discussed above, this assumption is incorrect in view of the evidence presented in the Specification.

Therefore, at best one of skill in the art would expect an additive effect, *i.e.*, the effect of GCSF (+1) and the effect of PlGF (0).

Thus, Applicants submit that this evidence is sufficient to rebut the any showing of *prima facie* obviousness which may be established by Hattori and Robinson. Instead:

(a) Example 2 shows that combining PlGF and GCSF results in a 1.4-fold increase in the frequency of CFCs over GCSF alone.

(b) Example 3 shows that combining PlGF and GCSF results in a 2-fold increase in the number of circulating CFCs over GCSF alone.

(c) Example 6 shows that combining PlGF and GCSF results in a 3.12-fold increase in the frequency of CFCs over GCSF alone when PlGF is at a high dose, and 2.73-fold increase when PlGF is at a lower dose.

(d) Example 7 shows that combining PlGF and GCSF results in a 4-fold increase in the absolute number of circulating CFCs over GCSF alone when PlGF is a high dose and 2.17-fold when PlGF is at a lower dose.

Applicants submit that these experiments demonstrate that the effect of the combination of GCSF and PlGF is unexpectedly higher than the administration of GCSF alone or PlGF alone. Applicants submit that there is no evidence in Hattori which suggests that this type of administration would be effective, because the Examiner relies on the administration of an Ad-PlGF which is not predictive of the effect of administration of PlGF protein, as discussed above. Accordingly, Applicants request that this rejection be withdrawn.

CONCLUSION

In view of the above remarks, it is believed that claims are allowable.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $1,110.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell Reg. No. 36,623 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: August 2, 2010

Respectfully submitted,

By _____

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Attachment: Rafii et al. (2002)